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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/463,549	01/27/2000	DANIEL HENRY DENSHAM	GJE-35	6468

23557 7590 11/18/2002

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EXAMINER	
CHAKRABARTI, ARUN K	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 11/18/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/463,549	Densham
Examiner	**Art Unit**
First Last	1234

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Oct 7, 2002* .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1, 3-21, 30-34, 36, and 37* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 3-21, 30-34, 36, and 37* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Detailed Action*

DETAILED ACTION

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 1, 3-9, 21, 30-34, and 36-37 are rejected under 35 U.S.C. 103 (a) over Tsien et al. (PCT International Publication NO: WO 91/06678) (May 16, 1991) in view of Holzrichter et al. (U.S. Patent 5,620,854) (April 15, 1997) further in view of Seeger (U.S. Patent 5,360,714) (November 1, 1994).

Tsien et al teach a method for sequencing a polynucleotide (Abstract), comprising the steps of :

(I) reacting a target polynucleotide with a polymerase enzyme and the different nucleotides, under conditions sufficient for the polymerase reaction (Abstract, Figures 1A, 1B and 2 and Example 3 and Claims 1-2); and

(ii) detecting an effect consequent on the incorporation of a specific nucleotide complementary to the target polynucleotide (Abstract, Claims 1, 7 and 12 and Example 4).

Tsien et al teach a method wherein the effect in step (ii) is detected by measuring radiation (Example 4).

Tsien et al teach a method wherein steps (I) and (ii) are conducted with each of the different nucleotides in turn, until incorporation is detected, and then repeated (Claims 49-50).

Tsien et al teach a method wherein step (I) is conducted with all the nucleotides present (Claim 4 and Figures 2 and 3).

Tsien et al teach a method wherein the nucleotides comprise a 3' blocking group which is removed after the polymerase reaction (Example 4 and Claims 3-5 and Figures 1-3).

Tsien et al teach a method wherein the blocking group can be selectively removed by pulsed monochromatic light (Page 25, lines 4-12).

Tsien et al teach a method wherein the nucleotide comprise a further blocking group at the terminal phosphate group of the triphosphate chain, and the further blocking group is removed prior to the removal of the 3' blocking group (Example 2).

Tsien et al inherently teach a method wherein the further blocking group can be selectively removed by pulsed monochromatic light under conditions and durations different from those required to remove the 3' blocking group (Page 25, lines 4-12).

Tsien et al inherently teach a method wherein the polynucleotide is DNA (Abstract and Figure 1).

Tsien et al do not teach a method wherein the polymerase enzyme is immobilized on a solid support.

Holzrichter et al. teach a method wherein the polymerase enzyme is immobilized on a solid support (Column 7, lines 22-28, abstract, Figure 2, and claims 1 and 11).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the polymerase enzyme immobilized on a solid support of Holzrichter et al. into the DNA sequencing method of Tsien et al , since Holzrichter et al. state, "The stationary mode of operation can be used to observe dynamic biological processes in real time and in a natural environment, such as polymerase processing of DNA for determining the sequence of a DNA molecule (Abstract, last sentence)." By employing scientific reasoning, an ordinary artisan would have combined and substituted the polymerase enzyme immobilized on a solid support of Holzrichter et al. into the DNA sequencing method of Tsien et al. in order to improve the analysis of a plurality of target nucleic acid. An ordinary practitioner would have been motivated to combine and substitute the polymerase enzyme immobilized on a solid support of Holzrichter et al. into the DNA sequencing method of Tsien et al., in order to achieve the express advantages noted by Holzrichter et al., of a method that provides advantages of stationary mode of operation that can be used to observe dynamic biological processes in real time and in a natural environment, such as polymerase processing of DNA for determining the sequence of a DNA molecule.

Tsien et al. in view of Holzrichter et al do not teach a nascent polynucleotide being synthesized as a result of the polymerase reaction wherein the complementary nucleotides are not labeled and the effect detected results from a conformation or mass change of the polymerase that occurs upon incorporation of the nucleotide.

Seeger teaches a nascent polynucleotide being synthesized as a result of the polymerase reaction wherein the complementary nucleotides are not labeled and the effect detected results from a conformation or mass change of the polymerase that occurs upon incorporation of the nucleotide (Column 3, line 26 to column 4, line 19, and Column 16, lines 1-6, and Claims 7, 16, and 18).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute a nascent polynucleotide being synthesized as a result of the polymerase reaction of Seeger into the DNA sequencing method of Tsien et al in view of Holzrichter et al., since Seeger states, "The composition and methods of the present invention will allow the screenings of many anti-viral compounds simultaneously with ease and rapidity. Moreover, quantitative results of the effect of each potential anti-viral agents are easily obtained (Column 4, lines 14-18)." By employing scientific reasoning, an ordinary artisan would have combined and substituted a nascent polynucleotide being synthesized as a result of the polymerase reaction of Seeger into the DNA sequencing method of Tsien et al in view of Holzrichter et al. in order to improve the analysis of a plurality of target nucleic acid. An ordinary practitioner would have been motivated to combine and substitute a nascent polynucleotide being synthesized as a result of the polymerase reaction of Seeger into the DNA sequencing method of Tsien et al in view of Holzrichter et al. in order to achieve the express advantages noted by Seeger, of a composition and methods that will allow the screenings of many anti-viral

compounds simultaneously with ease and rapidity and by which quantitative results of the effect of each potential anti-viral agents are easily obtained.

3. Claims 1, 3-9, 15, 17- 18, 21 and 30-34 are rejected under 35 U.S.C. 103 (a) over Tsien et al. (PCT International Publication NO: WO 91/06678) (May 16, 1991) in view of Holzrichter et al. (U.S. Patent 5,620,854) (April 15, 1997) further in view of Seeger (U.S. Patent 5,360,714) (November 1, 1994) further in view of Schwarz et al. (Trends in Biotechnology, (October ,1991), Vol. 9, pages 339-340).

Tsien et al in view of Holzrichter et al. in view of Seeger teach the method of claims 1, 3-9, 21 and 30-34 as described above.

Tsien et al in view of Holzrichter et al. in view of Seeger do not teach detection of nucleic acid incorporation by surface plasmon resonance signal over time in the infra-red spectrum.

Schwarz et al. teach the detection of nucleic acid incorporation by surface plasmon resonance signal over time in the infra-red spectrum (Figure 2 and Page 340, Columns 1-3).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the detection of nucleic acid incorporation by surface plasmon resonance signal over time in the infra-red spectrum of Schwarz et al. into the DNA sequencing method of Tsien et al in view of Holzrichter et al. further in view of Seeger, since Schwarz et al. state, "The particular advantages of SPR-based biosensors are (1) rapid reading and (2) real-time kinetic analysis. Detection sensitivity approaches that of conventional methods, and simple protocols can be used because probe labeling is unnecessary. The operation

of such biosensor is suitable for automation and can be developed to detect hybridizations of a sample to a number of DNA probes simultaneously (Page 340, Column 2, last three sentences)." By employing scientific reasoning, an ordinary artisan would have combined and substituted the detection of nucleic acid incorporation by surface plasmon resonance signal over time in the infra-red spectrum of Schwarz et al. into the DNA sequencing method of Tsien et al in view of Holzrichter et al further in view of Seeger in order to improve the analysis of a plurality of target nucleic acid. An ordinary practitioner would have been motivated to combine and substitute the detection of nucleic acid incorporation by surface plasmon resonance signal over time in the infra-red spectrum of Schwarz et al. into the DNA sequencing method of Tsien et al in view of Holzrichter et al. further in view of Seeger, in order to achieve the express advantages noted by Schwarz et al., of a method that provides advantages of SPR-based biosensors (1) rapid reading and (2) real-time kinetic analysis where probe labeling is unnecessary and the operation of such biosensor is suitable for automation and can be developed to detect hybridizations of a sample to a number of DNA probes simultaneously.

4. Claims 1, 3-10, 21 and 30-34 are rejected under 35 U.S.C. 103 (a) over Tsien et al . (PCT International Publication NO: WO 91/06678) (May 16, 1991) in view of Holzrichter et al. (U.S. Patent 5,620,854) (April 15, 1997) further in view of Seeger (U.S. Patent 5,360,714) (November 1, 1994) further in view of Chang et al. (U.S. Patent 5,801,042) (September 1, 1998).

Tsien et al in view of Holzrichter et al. further in view of Seeger teach the method of claims 1, 3-9, 21 and 30-34 as described above.

Tsien et al in view of Holzrichter et al. further in view of Seeger do not teach the competitive inhibitor of the polymerase enzyme.

Chang et al. teach the competitive inhibitor of the polymerase enzyme (Column 24, lines 25-60).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the competitive inhibitor of the polymerase enzyme of Chang et al. into the DNA sequencing method of Tsien et al in view of Holzrichter et al. further in view of Seeger, since Chang et al. state, "These nucleoside analogs act as competitive inhibitors of DNA polymerase substrates. The analogous may act as a chain terminator, cause increased lability (e.g., susceptibility to breakage) of analogue-containing DNA, and/or impair the ability of the substituted DNA to act as template for transcription or replication (Column 24, lines 47-60)." By employing scientific reasoning, an ordinary artisan would have combined and substituted the competitive inhibitor of the polymerase enzyme of Chang et al. into the DNA sequencing method of Tsien et al in view of Holzrichter et al. further in view of Seeger in order to inhibit the DNA polymerase to control and regulate the detection of the incorporated nucleotide. An ordinary practitioner would have been motivated to combine and substitute the competitive inhibitor of the polymerase enzyme of Chang et al. into the DNA sequencing method of Tsien et al. in view of Holzrichter et al. further in view of Seeger, in order to achieve the express advantages noted by Chang et al., of a competitive inhibitor of DNA polymerase substrates that may act as a chain terminator, cause increased lability (e.g.,

susceptibility to breakage) of analogue-containing DNA, and/or impair the ability of the substituted DNA to act as template for transcription or replication.

5. Claims 1, 3-9, 11-12, 21 and 30-34 are rejected under 35 U.S.C. 103 (a) over Tsien et al . (PCT International Publication NO: WO 91/06678) (May 16, 1991) in view of Holzrichter et al. (U.S. Patent 5,620,854) (April 15, 1997) further in view of Seeger (U.S. Patent 5,360,714) (November 1, 1994) further in view of O'Donnell (U.S. Patent 6,221,642 B1) (April 24, 2001).

Tsien et al in view of Holzrichter et al. further in view of Seeger teach the method of claims 1, 3-9, 21 and 30-34 as described above.

Tsien et al in view of Holzrichter et al. further in view of Seeger do not teach the beta-2 dimer complex of the E.coli DNA polymerase III with the target polynucleotide.

O'Donnell. teach the beta-2 dimer complex of the E.coli DNA polymerase III with the target polynucleotide (Abstract , Figure 1 and Column 4, lines 26-61).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the beta-2 dimer complex of the E.coli DNA polymerase III with the target polynucleotide of O'Donnell into the DNA sequencing method of Tsien et al in view of Holzrichter et al. further in view of Seeger, since O'Donnell states, "The beta clamp confers processivity onto the core polymerase by binding directly to the polymerase alpha subunit, thereby tethering the polymerase to DNA for processive syntheses (Column 4, lines 40-43)." O'Donnell further states, "This high degree of symmetry in the beta ring could help promote smooth gliding along the symmetrical DNA duplex (Column 4, lines 61-63)". By

employing scientific reasoning, an ordinary artisan would have combined and substituted the beta-2 dimer complex of the E.coli DNA polymerase III with the target polynucleotide of O'Donnell into the DNA sequencing method of Tsien et al in view of Holzrichter et al. further in view of Seeger, to improve the structure and function of the DNA polymerase. An ordinary practitioner would have been motivated to combine and substitute the beta-2 dimer complex of the E.coli DNA polymerase III with the target polynucleotide of O'Donnell into the DNA sequencing method of Tsien et al. in view of Holzrichter et al. further in view of Seeger, in order to achieve the express advantages noted by O'Donnell, of the beta clamp that confers processivity onto the core polymerase by binding directly to the polymerase alpha subunit, thereby tethering the polymerase to DNA for processive syntheses and also to achieve the advantage of the high degree of symmetry in the beta ring that could help promote smooth gliding along the symmetrical DNA duplex.

6. Claims 1, 3-9, 13, 21 and 30-34 are rejected under 35 U.S.C. 103 (a) over Tsien et al . (PCT International Publication NO: WO 91/06678) (May 16, 1991) in view of Holzrichter et al. (U.S. Patent 5,620,854) (April 15, 1997) further in view of Seeger (U.S. Patent 5,360,714) (November 1, 1994) further in view of Rosenthal et al. (PCT International Publication Number: WO 93/21340) (October 21, 1993).

Tsien et al in view of Holzrichter et al. further in view of Seeger teach the method of claims 1, 3-9, 21 and 30-34 as described above.

Tsien et al in view of Holzrichter et al. further in view of Seeger do not teach the Taq polymerase.

Rosenthal et al. teach the Taq polymerase (Page 9, lines 5-10).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the Taq polymerase of Rosenthal et al. into the DNA sequencing method of Tsien et al in view of Holzrichter et al. further in view of Seeger, since Rosenthal et al state, "Suitable DNA polymerases are, for example, Sequenase 2.0, T4 DNA polymerase or the Klenow fragment of DNA polymerase 1 as well as heat-stable polymerase such as Taq polymerase (for example Taquenase) (Page 9, lines 7-10)." By employing scientific reasoning, an ordinary artisan would have combined and substituted the Taq polymerase of Rosenthal et al. into the DNA sequencing method of Tsien et al in view of Holzrichter et al. further in view of Seeger, to improve the function of the DNA polymerase. An ordinary practitioner would have been motivated to combine and substitute the Taq polymerase of Rosenthal et al. into the DNA sequencing method of Tsien et al in view of Holzrichter et al. further in view of Seeger, in order to achieve the express advantages noted by Rosenthal et al., of suitable DNA polymerases for example, Sequenase 2.0, T4 DNA polymerase or the Klenow fragment of DNA polymerase 1 as well as heat-stable polymerase such as Taq polymerase (for example Taquenase).

7. Claims 1, 3-9, 14, 21 and 30-34 are rejected under 35 U.S.C. 103 (a) over Tsien et al . (PCT International Publication NO: WO 91/06678) (May 16, 1991) in view of Holzrichter et al.

(U.S. Patent 5,620,854) (April 15, 1997) further in view of Seeger (U.S. Patent 5,360,714) (November 1, 1994) further in view of Vind (U.S. Patent 6,159,687) (December 12, 2000).

Tsien et al in view of Holzrichter et al. further in view of Seeger teach the method of claims 1, 3-9, 21 and 30-34 as described above.

Tsien et al in view of Holzrichter et al. further in view of Seeger do not teach the reverse transcriptase as the polymerase.

Vind teaches the reverse transcriptase as the polymerase (Column 7, lines 15-21).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the reverse transcriptase as the polymerase of Vind into the DNA sequencing method of Tsien et al in view of Holzrichter et al. further in view of Seeger, since Vind states, "The choice of polymerase is therefore an important means in controlling the average extension of the primers. These conditions may also exert an influence on the fidelity of the polymerase (the rate by which point mutations are introduced; HIV reverse transcriptase is an example of a polymerase of low fidelity), a parameter useful in combining shuffling and mutagenesis (Column 7, lines 15-21)." By employing scientific reasoning, an ordinary artisan would have combined and substituted the reverse transcriptase as the polymerase of Vind into the DNA sequencing method of Tsien et al in view of Holzrichter et al. further in view of Seeger , to improve the function of the DNA polymerase and the sequencing of DNA. An ordinary practitioner would have been motivated to combine and substitute the reverse transcriptase as the polymerase of Vind into the DNA sequencing method of Tsien et al in view

of Holzrichter et al. further in view of Seeger, in order to achieve the express advantages noted by Vind, of the choice of polymerase which is an important means in controlling the average extension of the primers which also may exert an influence on the fidelity of the polymerase (the rate by which point mutations are introduced; HIV reverse transcriptase is an example of a polymerase of low fidelity), a parameter useful in combining shuffling and mutagenesis.

8. Claims 1, 3-9, 16, 19-21 and 30-34 are rejected under 35 U.S.C. 103 (a) over Tsien et al . (PCT International Publication NO: WO 91/06678) (May 16, 1991) in view of Holzrichter et al. (U.S. Patent 5,620,854) (April 15, 1997) further in view of Seeger (U.S. Patent 5,360,714) (November 1, 1994) further in view of Smith et al. (U.S. Patent 5,753,439) (May 19, 1998).

Tsien et al in view of Holzrichter et al. further in view of Seeger teach the method of claims 1, 3-9, 21 and 30-34 as described above.

Tsien et al in view of Holzrichter et al. further in view of Seeger do not teach the detection of nucleotides by NMR using electromagnetic radiation.

Smith et al. teach the detection of nucleotides by NMR using electromagnetic radiation (Column 7, lines 14-29).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the detection of nucleotides by NMR using electromagnetic radiation of Smith et al. into the DNA sequencing method of Tsien et al in view of Holzrichter et al. further in view of Seeger, since Smith et al. state, "These methods can be used to detect characteristic nucleic acid sequences, to determine target sequence and to screen

for genetic defects and disorders. Assays can be conducted on solid surfaces allowing for multiple reactions to be conducted in parallel and, if desired, automated (Abstract, last two sentences)." By employing scientific reasoning, an ordinary artisan would have combined and substituted the detection of nucleotides by NMR using electromagnetic radiation of Smith et al. into the DNA sequencing method of Tsien et al in view of Holzrichter et al. further in view of Seeger to improve the sequencing of DNA. An ordinary practitioner would have been motivated to combine and substitute the detection of nucleotides by NMR using electromagnetic radiation of Smith et al. into the DNA sequencing method of Tsien et al in view of Holzrichter et al. further in view of Seeger in order to achieve the express advantages noted by Smith et al., of the methods which can be used to detect characteristic nucleic acid sequences, to determine target sequence and to screen for genetic defects and disorders and which can be conducted on solid surfaces allowing for multiple reactions to be conducted in parallel and, if desired, automated.

Response to Arguments

9. Applicant's arguments filed on October 7, 2002 have been fully considered but they are not persuasive.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Applicant argues that there is no

motivation to combine the references. This argument is not persuasive especially in the presence of strong motivation provided by Holzrichter et al. since Holzrichter et al. states, "The stationary mode of operation can be used to observe dynamic biological processes in real time and in a natural environment, such as polymerase processing of DNA for determining the sequence of a DNA molecule (Abstract, last sentence)." The same logic is applicable to the reasoning of combination of all other references.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., the incorporation of a nucleotide into the reaction site of a polymerase during synthesis of a DNA strand complementary to the target DNA sequence results in an effect on the polymerase that can be detected by measuring radiation) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

In response to applicant's argument that Seeger is nonanalogous art, it has been held that a prior art reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention. See *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). In this case, Seeger clearly teaches the essential requirement of sequences of primers and inherently the sequences of the amplification products (Column 14, line 54 to Column 15, line 4).

Applicant then argues the 103 rejection is improper because it lacks a reasonable expectation of success.

With regard to the "lack of reasonable expectation of success" argument, The MPEP 2143.02 states "Obviousness does not require absolute predictability, however, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. In re Rinehart , 531 F.2d 1048, 189 USPQ 143 (CCPA 1976) (Claims directed to a method for the commercial scale production of polyesters in the presence of a solvent at superatmospheric pressure were rejected as obvious over a reference which taught the claimed method at atmospheric pressure in view of a reference which taught the claimed process except for the presence of a solvent. The court reversed, finding there was no reasonable expectation that a process combining the prior art steps could be successfully scaled up in view of unchallenged evidence showing that the prior art processes individually could not be commercially scaled up successfully.). See also Amgen, Inc. v. Chugai Pharmaceutical Co ., 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir.), cert. denied , 502 U.S. 856 (1991) (In the context of a biotechnology case, testimony supported the conclusion that the references did not show that there was a reasonable expectation of success. 18 USPQ2d at 1022, 1023.); In re O'Farrell , 853 F.2d 894, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988) (The court held the claimed method would have been obvious over the prior art relied upon because one reference contained a detailed enabling methodology, a suggestion to modify the prior art to produce the claimed invention, and evidence suggesting the modification would be successful.)."

There is no evidence of record submitted by applicant demonstrating the absence of a reasonable expectation of success. There is evidence in the Tsien reference of the enabling methodology, the suggestion to modify the prior art, and evidence that a number of different DNA molecules were actually experimentally sequenced and found to be functional (Example 7). This evidence of functionality trumps the attorney arguments, which argues that combination of reference is an invitation to research, since Tsien steps beyond research and shows the functional product.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Applicant also argues that none of the references teach the change in conformation or mass of the polymerase. This argument is not persuasive. It is well known in the art to an ordinary practitioner that during an enzyme reaction, the enzyme binds to substrate to form a complex and then dissociated to form the substrate, thereby inherently undergoing conformation change during the reaction. In this case, polymerase enzyme necessarily and inherently undergoes the same process, thereby attributing to configurational change. The measured product (no matter

by what process it is measured) is therefore an inherent measurement of the configurational change of the enzyme during the reaction.

Applicant also argues that Seeger reference teaches an additional step of measuring the amount of the nascent DNA strand, not required by the instant invention. This argument is not persuasive. Applicant is hereby notified that in presence of "comprising" language of the instant claims any additional step(s) or materials can be included in the instant invention.

In response to arguments, all 103(a) rejections made in the last office action are hereby properly maintained.

Conclusion

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Arun Chakrabarti, Ph.D., whose telephone number is (703) 306-5818. The examiner can normally be reached on 7:00 AM-4:30 PM from Monday to Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for this Group is (703) 305-7401.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group analyst Chantae Dessau whose telephone number is (703) 605-1237.

Arun Chakrabarti,

Patent Examiner,

November 14, 2002

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600